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10/729,056	12/05/2003	David J. Grainger	295.009US4	9616

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,056	GRAINGER ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *153,154,157-165 and 169-176* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *153, 154, 157-165, 169-176* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/13/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/13/2008 has been entered.

Claims 153, 154, 169 has been amended and claims 1-152, 155, 156, 166-168 has been cancelled. Claims 174-176 have been added new. Claims 153, 154, 157-165, 169-176 are currently pending and are being examined on the merits herein.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 153, 154, 157-165, 169-175 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 173-194,196-203, 205-211 and 231 of copending Application No. 09/754,775. Although the conflicting claims are not identical, they are not patentably distinct from

each other because the copending application teaches an aspect of the claims in the instant application. For example, the method claimed in claims 153, 154, 157-165, 169-175 of the instant application utilizes the same biological pathway comprising increasing the level of TGF-beta encompassing utilizes the same active agents in the method of claim 173 of the co-pending application. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the diseases and the agents claimed in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 153, 154, 157-165, 169-176 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 153, 154, 157-165, 169-176 are drawn to a method of inhibiting or treating a vascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct

formation relative to tamoxifen b) administering a cytostatic dose of the agent to a mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof. The claim thus encompass a broad genus of an agent that directly or indirectly elevates the level of active TGF-beta in said mammal, wherein the agent which must have the property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination thereof. The claims also indicate administering a cytotoxic dose of such agents to a mammal with decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis.

The instant specification does not describe or exemplify all agents which must have the property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination thereof. The specification does not teach administration of such agent(s) to a mammal in general or to a to a mammal with decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis.

This instant specification, therefore, does not provide a basis for one of skill in the art to envision any one of such agents. There is no basis to predict **any agent** having a particular property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination thereof.

Given the broad of genus of **an agent** having the property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to

tamoxifen encompassed by the rejected claim, and given the lack of a basis provided by instant specification or prior art to envision such agents that are necessary capable of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination thereof, one of skill in the art would not have been able to envision a sufficient number of an agents possessing the property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination of characteristics thereof to describe broadly claimed genus. Therefore, one of skill in the art would reasonably have concluded Applicants' were not in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 153-155, 157-168 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for inhibiting a vascular indication in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required

undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a therapeutic method for inhibiting or treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof.

(2) Breadth of the Claims:

The instant claims are broad and embrace inhibiting or treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or

thrombosis so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof.

(3) Guidance of the Specification:

The guidance of the specification towards the inhibiting of cardiovascular indication administering TGF-beta agent is completely lacking. The instant specification does not describe or exemplify all agents which must have the property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination thereof. The specification does not teach administration of such agent(s) to a mammal in general or to a to a mammal with decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis.

(4) Working Examples:

Applicant does not provide any working examples for inhibiting cardiovascular indication administering TGF-beta agent that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen in a mammal.

(5) State/predictability of the Art:

The state of the art regarding treating a cardiovascular indication administering TGF-beta agent that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen in a mammal is relatively high. Inhibition is defined as " interference with or retardation or prevention of a process or activity" (http://medical.merriam-webster.com/medical /inhibition) However, the state of the art for inhibiting or preventing cardiovascular indication administering TGF-beta agent in a mammal is underdeveloped. It is highly unpredictable from the art that the

administration of above said agents which completely inhibit (prevent) a cardiovascular indication.

(6) The Quantity of Experimentation Necessary:

The instant claims read on the inhibiting of cardiovascular indication administering TGF-beta agent that has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen in a mammal. The instant specification does not describe or exemplify all agents which must have the property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination thereof. The specification does not teach administration of such agent(s) to a mammal in general or to a mammal with decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis. The specification fails to provide sufficient support for completely protecting a mammal against vascular indication. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly the claims are evaluated as a method for treating a vascular indication in a mammal and not as a method for inhibiting a vascular indication in a mammal.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 153, 154, 160, 158, 165, 169, 170, 174, 175 are rejected under 35 U.S.C. 102(b) as being anticipated by Connolly et al. (U.S.Patent No. 5,250,561).

Connolly et al. teach that tetrahydroindazole compounds are useful in treatment or inhibiting of hypercholesterolemia and atherosclerosis.

The instantly claimed "an agent" to be employed is encompassed by this teaching because the tetrahydroindazole compound disclosed by Connolly et al. has no estrogenic activity which meets the requirement of the agent having reduced estrogenic activity relative to tamoxifen. Further, the mechanism of action of increasing the level of TGF-beta gives the pharmacological effect does not alter the fact that the compound (an agent having property of reduced estrogenic activity relative to tamoxifen) has been previously used to obtain the same pharmacological effects (atherosclerosis) which would result from the claimed method. The patient, condition to be treated and the effect are the same. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 153-154, 157-162, 165, 169-172, 174-176 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morisake et al. (Atherosclerosis, 88, 1991, 227-234) in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and further in view of Kangas, (Breast Cancer Res Treat, 1990, Aug 16, S 3-7).

Morisake et al. teach that transforming growth factor TGF-beta is secreted by many types of cells including platelets and macrophages and these cells are closely related to the formation of atherosclerosis and that TGF-beta may play an important role in the development of atherosclerosis and has been found to influence the proliferation of aortic smooth muscle cells 9 P 227- para 1 to p 228, col. 1, lines 1-6). The reference further teaches that TGF-beta 1 inhibits cell proliferation of quiescent subconfluent smooth muscle cells (p 229, col. 2, lines 5-7, Discussion, para 2, lines 1-3). In summary, the reference teach that TGF-beta is useful in the treatment of atherosclerosis because it has been shown to inhibit the proliferation of smooth muscle cell along the blood vessel, which is the cause if atherosclerosis.

The reference does not teach an agent such as toremifene elevates TGF-beta level.

Knabbe et al. teach the induction of transforming growth factor beta by the antiestrogen toremifene (See Abstract).

The references do not explicitly teach that toremifene have reduced estrogenic activity.

Kangas teach that antiestrogenicity/estrogenicity ratio of toremifene in animal models is about 5 times that of tamoxifen (See Abstract). The reference teaches administration of 60 mg daily dose in humans (p S-5, col.1, lines –4, pharmacokinetics and metabolism of toremifene in humans).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have selected an agent that elevates TGF-beta level in a method of treating atherosclerosis or to inhibit the smooth muscle cell proliferation because of the teachings of Morisake et al. Morisake et al. teach that TGF-beta is useful in the treatment of atherosclerosis because it has been shown to inhibit the proliferation of smooth muscle cell along the blood vessel, which is the cause if atherosclerosis. Knabbe et al. teach the induction of transforming growth factor beta by the antiestrogen toremifene. One having ordinary skill in the art at the time of the invention would have been motivated to select an agent such as toremifene and administer to inhibit smooth muscle cell proliferation in expectation of success as well in effectively treating atherosclerosis. The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of

administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results.

The references do not teach that the patient is subjected to procedure vascular trauma and the agent toremifene decreases smooth cell proliferation associated with procedural vascular trauma. It would have been obvious to one of ordinary skill in the art at the time of the invention from the teachings of Morisake et al. and Knabbe et al that inhibition of smooth muscle cell proliferation occurs after administration of an agent that elevates TGF-beta level as Knabbe et al. teaches the induction of TGF-beta with toremifene and Morisake et al. teach inhibition of smooth muscle cell proliferation in presence of TGF-beta. It would have been obvious from the teachings of Morisake et al. that TGF-beta will inhibit smooth muscle proliferation irrespective of patients being subjected to vascular trauma or procedure. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 163 and 173 are rejected under 35 U.S.C. 103(a) as being unpatentable Morisake et al. (Atherosclerosis, 88, 1991, 227-234) in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and further in view of Kangas, (Breast Cancer Res Treat,

1990, Aug 16, S 3-7) as applied to claims 153-154, 157-162, 165, 169-173 above and further in view of Warri et al. (J Natl Cancer Inst. 1993, 85, 17, 1412)

Morisake et al, Kangas and Knabbe's teachings discussed as above.

The references do not teach that the agent toremifene increases the production of TGF-beta mRNA.

Warri et al. teach that elevated TGF beta 1 mRNA was observed in vitro and in vivo grown tumor cells treated with toremifene (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention that toremifene increased or elevated the production of mRNA because of the teachings of Warri et al. The reference teaches that treatment with toremifene increased TGF beta 1 mRNA levels in vitro and in vivo grown tumor cells.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable Morisake et al. (Atherosclerosis, 88, 1991, 227-234) in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and further in view of Kangas, (Breast Cancer Res Treat, 1990, Aug 16, S 3-7) as applied to claims 153-154, 157-162, 165, 169-173 above and further in view of Cullinan et al. (U.S. 5,457,113).

Morisake et al, Kangas and Knabbe's teachings discussed as above.

The references do not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent as to inhibit smooth cell proliferation to treat atherosclerosis as taught by Morisake et al. because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit smooth cell proliferation to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been considered but are moot in view of the new grounds of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
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